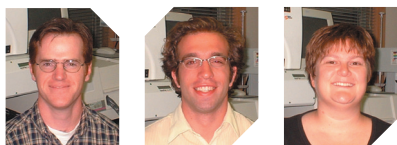




Controlled Delivery Technologies Applied to the Nutraceutical Industry



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Medical professionals and consumers are increasingly viewing nutraceuticals as adjuncts to traditional, pharmaceutical-based therapeutics. The growing awareness of the therapeutic potential of nutraceuticals has prompted the application of pharmaceutical controlled delivery technologies to the nutraceutical industry. While controlled release nutraceuticals have thus far developed to a limited extent for both economic and technical reasons, delivery technologies are being developed to adapt to the unique demands of the nutraceutical market.

Controlled delivery technologies refer to the process of engineering control over the release of a given active ingredient from a device such as a capsule or tablet during its transit through the gastrointestinal tract. Some common terms that are associated with controlled delivery are 'timed', 'extended', 'sustained' and 'prolonged' release. While not all products which use these terms are identical in their rate and extent of release, they are distinguished from 'immediate' release products that do not contain any mechanism for controlling the release of the active ingredient.

The vast majority of nutraceuticals are immediate release products that rapidly dissolve in the stomach once swallowed. Rapid dissolution may effect the nutraceutical's active ingredient in one or more ways, including changes in solubility or structure due to the acidic pH and enzymes of the gastric fluid. This may result in an insufficient amount of the active agent being absorbed or the compound being cleared from the body before the next scheduled dose, leaving the consumer without the therapeutic benefit of the nutraceutical in the interim. With many immediate release products, the only means of adapting to this cycle of 'rapid dissolution – rapid clearance' is to take multiple doses throughout the day, which may result in decreased consumer compliance such as skipped doses or discontinued product use.

Controlled delivery technologies can ameliorate many of these issues by reducing dosing frequency, allowing for gastric bypass or site-specific delivery, increasing the efficacy of the active compound and improving safety through a reduction in side effects and breakthrough symptoms.

THE THERAPEUTIC WINDOW

An essential concept involved in the formulation objectives of controlled delivery is the 'therapeutic window'. When a

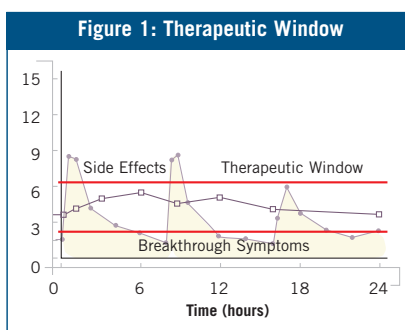
nutraceutical or pharmaceutical tablet or capsule is swallowed, the amount of agent absorbed may be measured as a concentration of active agent in the bloodstream (often referred to as a plasma level). In its simplest form, the therapeutic window is the range of concentration that results in optimal therapeutic effect – concentrations above this range may result in side effects and below this range may result in decreased efficacy, manifested by 'breakthrough symptoms', or a return of the symptoms the consumer is attempting to alleviate by taking a given nutraceutical.

The object of many controlled release technologies is to minimise the time during which the concentration of active ingredient is above or below the therapeutic window, while extending the duration of the active agent's existence within the efficacious range of concentration.

For active agents that display a relatively high solubility in water, are well absorbed, and possess a short plasma half-life, an immediate release product will result in a rapid increase in concentration of the active ingredient in the blood, followed by a rapid decrease in concentration as the agent is cleared from the body. This may be described as a 'peak and trough' effect – the peak is a concentration of higher amplitude than the therapeutic window while the trough is a concentration below the amplitude of the therapeutic window. An active agent that behaves in this manner and requires multiple doses throughout the day will display a series of these peaks and troughs each time the product is administered. This may result in the consumer experiencing dramatic onset and dramatic withdrawal of the active agent's effects.

Nutraceuticals such as caffeine and ephedrine provide excellent examples of this pattern: an immediate release caffeine tablet (equivalent to a single cup of coffee) provides the consumer with a stimulant effect that should dissipate quickly after three to four hours. To regain the stimulant effect, another dose must be taken; to maintain the stimulant effects throughout the entire day, multiple doses must be taken. This represents a standard peak and trough pattern. If a larger dose of caffeine is taken, the stimulant effect is increased during the initial hour, but may be accompanied by side effects associated with caffeine such as anxiety, nervousness or tachycardia, and when this larger dose is cleared from the system a more pronounced return of the symptomology – lack of energy, headaches – is experienced by the consumer. These extreme peak

Delivery Type	Advantages	Disadvantages
Osmotic pump	Release is independent of environment, very reproducible <i>in vivo</i>	Very complex to manufacture; low drug load (<200mg)
Multi-particulate	Amenable to poorly flowing active ingredient, capsule friendly	Low drug load, potential for incomplete release
Pore forming wax matrix	Cost-effective; no specialised equipment required	Little patent protection, few capable of 24 hour release
Physical-geometrical	Easy patent enforcement, unique release profiles	Complex to manufacture, variability <i>in vivo</i>
Diffusion matrix	Cost-effective; capable of a variety of release profiles	Few capable of high drug load, limited to high-solubility actives



and trough effects represent the potential consequences of a dose above or below the therapeutic window; in the case of some stimulants such as ephedra, these side effects have caused increased concern over product safety. A controlled release formulation might allow for a more constant rate of release from the dosage form, providing a stimulant effect throughout the course of the day with only a single dose, decreasing potential side effects and improving the safety of the product.

PRODUCT LIFE CYCLE MANAGEMENT

The high cost and extended development times of pharmaceutical markets require extensive life cycle management. The nature of the nutraceutical industry has allowed for a much lower cost of product development, but has traditionally featured a dramatically shorter product life. With the expansion of the nutraceutical market, manufacturers who extend a successful product’s market life or are the first to market with a more efficacious, convenient or safer product may experience significant benefits over their competitors.

The application of controlled delivery technologies to increase market share and add flexibility to the life cycle management of nutraceuticals follows three main strategies: line extensions of existing immediate release products; product differentiation through technological advantage; and intellectual property development. Immediate release products that require multiple daily doses due to high solubility and short plasma half-life are excellent candidates for controlled release formulations that slow the rate at which the active agent enters solution (the dissolution rate). For those active agents whose absorption is dependent on a saturable transport mechanism, slowing their dissolution rate may allow for a smaller dose than the immediate release preparation. Since many compounds are poorly soluble in water, delivery technologies may also be employed to enhance the solubility of the active agent, potentially allowing for the administration of a smaller dose. Tangible benefits to the consumer such as reduced side effects, less frequent dosing, and smaller tablet or capsule size provide a technological advantage and product differentiation improving consumer compliance and increase market share.

The widespread use of non-branded nutraceutical compounds heightens the importance of product differentiation, and the development of an intellectual property portfolio can enhance manufacturers’ ability to protect and further accelerate gains in market share. A patented delivery system allows for the protection of an unbranded or non-proprietary compound, additional protection of a branded or proprietary compound, or an extension of a currently patented compound nearing the end of its patent life. The application of a patented delivery system generates an intellectual property portfolio driven by formulation and

utility patents, creating a stronger barrier to competition and providing the opportunity for external licensing agreements.

The large number of candidate immediate release products and the variety of controlled delivery technologies available prompt the manufacturer to consider the impact of both pharmacologic and

economic factors when evaluating the development cost of a controlled release nutraceutical product. Ultimately, the costs of developing a controlled release product need to be offset by reducing market erosion, gaining market share or improving margins through premium pricing. The ability of a controlled delivery technology to recoup these costs depends largely on the consumer’s recognition of the benefits of a product, the ability of a manufacturer to educate the consumer about these benefits and the protection gained from competitors afforded by legal barriers, such as patents and exclusivity agreements.

FAVOURABLE CHARACTERISTICS OF CONTROLLED DELIVERY TECHNOLOGIES

The price-sensitive nature of the nutraceutical market demands that a controlled delivery technology display cost-effectiveness, robustness, ruggedness and flexibility both in the process of manufacture and *in vivo* performance, and provide some degree of patent protection. This limits the scope of delivery technologies that may be cost-effectively transferred directly from the pharmaceutical industry, yet also drives the development of novel delivery technologies dedicated to price-sensitive markets such as nutraceuticals and generic pharmaceuticals.

Optimally, the manufacture of a controlled delivery product should be as similar as possible to the process of manufacturing the current immediate release product. Controlled release technologies that can be optimised on existing equipment and processes do not require expensive capital investment in equipment. The demonstration of reproducible performance from the bench to production will also allow for a much faster time to market, as well as resulting in reduced development costs. Complex delivery technologies that require specialised processing equipment, non-standard excipients or multiple processing steps can also significantly increase the cost of manufacture.

The ruggedness of a controlled delivery system is a fundamental variable in determining the economic viability of a product. Excessive sensitivity to variations between manufacturing equipment – blenders, tablet presses, encapsulators – is undesirable because of the cost-advantages of a transferable and multi-site friendly manufacturing process. Independence from minor changes in formulation and manufacturing processes is a distinct advantage due to the raw material vendor changes common in the nutraceutical market. Resilience to environmental changes is also an advantageous characteristic due to lack of universal climate control in all manufacturing facilities; cGMP manufacturing conditions alleviate the vast majority of climate variations, but sensitivity to environmental impact upon raw materials and finished product shipment may still impact less-robust systems.

Because a controlled delivery technology is being relied upon to release the active ingredient at a reproducible rate and extent over an extended timeframe, the robustness of the final controlled delivery product is of unique importance compared to a similar immediate release product. Dissolution performance of a controlled delivery technology may be affected by temperature, agitation (hydrodynamics), media viscosity and solvent characteristics among other factors. A delivery system that fails to control the release of an active ingredient, or conversely fails to completely release the active compound when exposed to increased agitation or physiological shifts in pH, may result in the finished product performing non-reproducibly *in vivo*.

The flexibility of a controlled delivery system is important to both manufacturing processes and finished product performance. The ability to formulate geometrically scaled dosages with reproducible performance is a considerable advantage when developing multiple dosage-strength line extensions from existing products. Controlled delivery technologies which permit a relative ease of formulation provide the manufacturer with increased flexibility for line extensions of the controlled release products themselves; subsequent generations of a first-order release product might feature delayed onset, bi-modal or zero-order release.

ACHIEVING CONTROLLED DELIVERY OF NUTRACEUTICAL PRODUCTS

Solid oral controlled delivery technologies consist of five generalised platforms: reservoir, physical-geometric, multi-particulate, poreforming wax and diffusion matrices. Other controlled delivery devices such as transdermal patches, aerosol inhalers and liquid micro-emulsions and suspensions are also used in pharmaceutical drug delivery, but are not yet applicable to the nutraceutical industry due to their rigorous development requirements and intricate manufacturing process.

Reservoir and physical-geometric platforms are less applicable to the nutraceutical industry, largely due to the complexity of manufacture relative to comparable oral delivery technologies. A basic embodiment of a reservoir system is a variation of a classic push-pull osmotic system, (for example OROS[®], Alza Corp), in which the active ingredient is pushed into the gastrointestinal tract as aqueous solution is absorbed into the tablet. Though widely utilised in the pharmaceutical industry due to its reproducible and programmable release profile, its manufacturing process requires specialised equipment and multiple production steps, low drug load and potentially difficult scale-up results in a relatively low utility for osmotic membrane nutraceutical controlled delivery products.

Physical-geometric delivery technologies face similar barriers to the nutraceutical market. These manufacturing processes involve multiple components for a single dosage form, such as a series of tablets within a capsule (for example GEOMATRIX[®], SkyePharma Corp), and may feature a large amount of variability during *in vivo* dissolution, resulting in an unbalanced cost-benefit ratio to consumers for all but a narrow sector of the nutraceutical market.

Multi-particulate or coated bead systems are adept at achieving the flexibility of release profiles exhibited in physical-geometric devices at potentially lower development costs. These systems coat, blend or granulate the active ingredient with polymers to modify release rates due to the differing erosional and diffusional

characteristics among the beads. Being capsule friendly, multi-particulate systems may be applicable to low-dose nutraceuticals with poor flow and tableting properties. However, multi-particulate systems are relatively complex to manufacture requiring a large number of excipients, frequently including solvents and contributing to a lengthy processing time.

The most economical delivery technology, with low production cost and ready manufacturing, pore forming wax matrices are widely employed throughout the OTC and generic pharmaceutical industry. Wax or wax-like compounds such as paraffin or guar gum are granulated with the active ingredient and water-soluble polymers and other excipients that will dissolve when exposed to gastrointestinal fluid, leaving pores through which the active agent may be released. Because the rate of release in wax matrix systems is dependent on erosion of the matrix and the diffusion characteristics of the active agent, they are often not capable of complex release profiles or once per day dosing.

Diffusion systems offer a combination of economy and performance, frequently consisting of a monolithic tablet containing the active ingredient and one or more hydrophilic polymers. They allow for the controlled penetration of water and the subsequent swelling of the hydrophilic polymers, releasing the active agent through the resulting gel-phase through a combination of diffusion and erosion. The active ingredient may be granulated with other polymers to create the desired release profile – adding processing steps and their associated costs to the manufacturing process. The range and scope of nutraceuticals that may be employed in diffusion systems is considerably larger than other technologies, yet often excludes exceptionally high solubility, high dose nutraceuticals due to the large volume of polymer and the correspondingly large tablet size required to achieve control.

Hybrid systems combining aspects of each category of release mechanism have developed in an attempt to create more cost-effective and versatile delivery systems. Multi-particulate systems may be combined with polymeric or wax matrices to create hybrid diffusion or wax-based systems. Modified diffusion matrix systems may be formulated using novel combinations of polymers and excipients to alter gel-phase characteristics. These modified diffusion systems allow for a much greater flexibility in designing unique release rates and reproducing the release profiles of the more complex osmotic membrane or geometric-physical systems, while maintaining the robustness, ruggedness and cost-effectiveness of diffusion systems.

The cost-effective application of controlled delivery technologies will play a major role in the expansion of the nutraceutical industry through their ability to improve on the performance of immediate release products in a manner tangible to consumers. Less frequent dosing and reductions in side effects will benefit both consumers and manufacturers as safer, more convenient and efficacious products become the standard for the industry. Increasing consumer compliance and product differentiation will enable the expansion of the premium-pricing market, and the development of intellectual property portfolios will allow manufacturers to more readily acquire and defend market share. ♦

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